

Form PTO 1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV 5-93)		ATTORNEY'S DOCKET NUMBER P50464-1
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, enter in Case No.) 09/142983
INTERNATIONAL APPLICATION NO. PCT/US97/04876	INTERNATIONAL FILING DATE 26 March 1997	PRIORITY DATE CLAIMED 26 March 1996
TITLE OF INVENTION PLA2 INHIBITORS OF ANGIOGENESIS		
APPLICANT(S) FOR DO/EO/US Jeffrey R. JACKSON and James D. WINKLER		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:


091898 091898

US APPLICATION NO. (if known see 37 CFR 1.50)		INTERNATIONAL APPLICATION NO. PCT/US97/04876		ATTORNEYS DOCKET NO. P50464-1	
17. <input checked="" type="checkbox"/> The following fees are submitted:				CALCULATIONS PTO USE ONLY	
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):					
Search Report has been prepared by the EPO or JPO\$930.00					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482)\$720.00					
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))\$790.00					
Neither International Preliminary Examination Fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$1070.00					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....\$98.00					
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$98.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than o 20 o 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$0.00	
Claims	Number Filed	Number Extra	Rate		
Total claims	6-20	0	0 x \$22.00	\$0.00	
Independent claims	1-3 =	0	0 x \$82.00	\$0.00	
Multiple dependent claims (if applicable)			+ \$270.00	\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$98.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$	
SUBTOTAL =				\$98.00	
Processing fee of \$130.00 for furnishing the English translation later than o 20 o 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				\$	
TOTAL NATIONAL FEE =				\$98.00	
				Amount to be refunded	\$
				charged	\$

- a. A check in the amount of \$_____ to cover the above fees is enclosed.
- b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **\$98.00** to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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IN THE UNITED STATES INTERNATIONAL EXAMINING AUTHORITY

International Application No.: PCT/US97/04876
International Filing Date: 26 March 1997
Priority Date Claimed: 26 March 1996
Applicants for DO/US: Jeffrey R. JACKSON and James D. WINKLER
Title of Invention: PLA2 INHIBITORS OF ANGIOGENESIS
Assistant Commissioner for Patents
Box PCT
Washington D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Preliminary to examination of this application, please enter the following amendment:

In the Specification:


Page 1, under the title, please enter the following:

--This application is the §371 National Stage entry of PCT/US97/04876, filed 26 March 1997 which claims the benefit of priority from provisional application USSN 60/014,244 filed 26 March 1996.--

REMARKS

This Preliminary Amendment is being made upon entry of International Application No. PCT/US97/04876 into the U.S. national phase of prosecution.

Respectfully submitted,



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PLA₂ Inhibitors of Angiogenesis

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FIELD OF THE INVENTION

The present invention relates to the treatment of diseases, in a mammal, in which inappropriate, excessive or undesirable angiogenesis has occurred.

10 **BACKGROUND OF THE INVENTION**

Chronic diseases are often accompanied by profound angiogenesis, which can contribute to or maintain an inflammatory and/or proliferative state, or which leads to tissue destruction through the invasive proliferation of blood vessels. IL-1 β and TNF α have been found to be potent inducers of angiogenesis *in vivo* and are commonly involved in the pathology of chronic inflammatory diseases (Folkman and Shing, J. Biol. Chem. 267:10931, 1992).

Angiogenesis is generally used to describe the development of new or replacement blood vessels, or neovascularisation. It is a necessary and physiologically normal process by which the vasculature is established in the embryo. Angiogenesis does not occur, in general, in the normal adult. Many diseases, however, are characterized by persistent and unregulated angiogenesis. For instance, in arthritis, new capillary blood vessels invade the joint and destroy cartilage (Colville-Nash and Scott, Ann. Rheum. Dis., 51, 919, 1992). In diabetes, new vessels invade the vitreous and blood, and cause blindness (and may occur in many different eye diseases) (Brooks et al., Cell, 79, 1157, 1994). The process of atherosclerosis has been linked to angiogenesis (Kahlon et al., Can. J. Cardiol. 8, 60, 1992). Tumor growth and metasis have been found to be angiogenesis-dependent (Folkman, Cancer Biol. 3, 65, 1992; Denekamp, Br. J. Rad. 66, 181, 1993; Fidler and Ellis, Cell, 79, 185, 1994).

The recognition of the involvement of angiogenesis in major diseases has been accompanied by research to identify and develop inhibitors of angiogenesis. These inhibitors are generally classified in response to discrete targets in the angiogenesis cascade, such as activation of endothelial cells by an angiogenic signal; synthesis and release of degradative enzymes; endothelial cell migration; proliferation of endothelial cells; and formation of capillary tubules. Therefore,

angiogenesis occurs in many stages and attempts are underway to discover and develop compounds that work to block angiogenesis at these various stages.

There are publications that teach that inhibitors of angiogenesis, working by diverse mechanisms, are beneficial in diseases such as cancer and metastasis (O'Reilly et al., Cell, 79, 315, 1994; Ingber et al., Nature, 348, 555, 1990), ocular diseases (Friedlander et al., Science, 270, 1500, 1995), arthritis (Peacock et al., J. Exp. Med. 175, 1135, 1992; Peacock et al., Cell. Immun. 160, 178, 1995) and hemangioma (Taraboletti et al., J. Natl. Cancer Inst. 87, 293, 1995).

A need still exists, however, to find suitable small molecule inhibitors which will block angiogenesis in a mammal for treatment of these diseases which have an angiogenic component. The current application teaches the novel finding that compounds that block cytokine production, can block angiogenesis by removing the early cytokine signals for angiogenesis.

15 SUMMARY OF THE INVENTION

The present invention is to the novel use of a PLA₂ inhibitor for the treatment of chronic inflammatory or proliferative or angiogenic diseases which are caused by excessive, inappropriate angiogenesis.

20 BRIEF DESCRIPTION OF THE DRAWINGS

Figure I A and B show the effect of Compound I in vascular casting model of angiogenesis, with IA showing vascular index, and IB showing granuloma dry weight.

25 DETAILED DESCRIPTION OF THE INVENTION

The present invention is to the novel use of a PLA₂ inhibitor, in particular that of low molecular weight, 14 kDa PLA₂, for the treatment of chronic inflammatory diseases which are caused by excessive or inappropriate angiogenesis.

Phospholipase A₂'s (PLA₂ (EC 3.1.1.4)) are responsible for the liberation of arachidonic acid from the sn-2 position of phospholipid. They are thought to play an important role in the pathogenesis of inflammation and possibly in immunological dysfunction, both as a cell associated enzyme as well as an extracellular soluble enzyme. Low molecular weight, mammalian Type II 14 kDa PLA₂ has been well characterized and is known to exist in both an extracellular form in inflammatory fluids (Kramer et al., J. Biol. Chem., 264:5768-5775 (1989) and in a cell associated form (Kanda et al., Biochemical and Biophysical Research Communications, 163:42-

48 (1989) and has been found in a variety of cells and tissues or extracellularly when released in response to antigenic activators or pro-inflammatory mediators such as Interleukin (IL)-1, IL-6 or tumor necrosis factor (TNF). Its presence in such inflammatory fluids, tissue exudates or serum has therefore implicated Type II-14 kDa-PLA₂'s role in inflammation (Vadas, et al., (1985) Life Sci. **36**, 579-587; and Seilhamer, et al., (1989) J. Biol. Chem. **264**, 5335-5338). Recently, the elevated serum levels of PLA₂ activity during an inflammatory insult has been attributed to cytokine induction of acute phase protein release from liver, of which the 14 kDa-PLA₂ is suggested to be a part (Cowl, et al., (1991) J. Biol. Chem. **266**, 2647-2651). In addition, soluble PLA₂ activity is markedly elevated in the serum and synovial fluid of patients with rheumatoid arthritis (Stefanski et al., J. Biochem. **100**:1297-303 (1986). Furthermore, increasing serum PLA₂ levels have been shown to positively correlate with clinical severity (Bomalaski and Clark, Arthritis and Rheumat. **36**:190-198 (1993)). Various inhibitors of PLA₂ have been described in publications and in US Patents. See for instance US Patents 4,959,357; 4,933,365; 5,208,223; 5,208,244; Marshall et al., J. Rheumatology **18**:1 (1991); Marshall et al., Phospholipase A₂, Ed. Pyu Wong, Plenum Press, NY (1990) pages 169-181; Wilkerson, et al., Eur. J. Med. Chem., **26**:667, 1991 and Wilkerson, Antiinflammatory Phospholipase A₂ Inhibitors, Drugs of the Future, Vol. **15**, No. 2 p 139-148(1990). Accordingly, as PLA₂ is important in the liberation of arachidonic acid from phospholipid and may also play a role in the generation of PAF via lysophospholipid formation, inhibition of such an enzyme would be useful for the treatment of disease states caused thereby.

There are many novel forms of phospholipase A₂'s which have recently been discovered. For the purposes herein, members of the sn-2 acylhydrolase family of PLA₂'s are divided into low and high molecular weight enzymes be it from mammalian, or non-mammalian sources. Low molecular weight PLA₂'s will generally have a molecular weight in the range of 12,000 to 15,000. High molecular weight will be in the range of 30,000 or 56,000 kDa to 110,000 by SDS electrophoresis analysis.

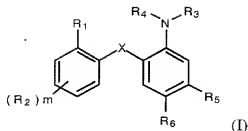
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30 generally have a molecular weight in the range of 12,000 to 15,000. High molecular weight will be in the range of 30,000 or 56,000 kDa to 110,000 by SDS electrophoresis analysis.

Preferred compounds for use herein as PLA₂ inhibitors include those compounds of Formula (I) represented by the structure:



wherein

R_1 is $(CH_2)_nOH$ or $(CH_2)_nCO_2R_8$;

n is 0 or an integer a value of 1;

5 X is oxygen or sulfur;

R_2 is hydrogen, halogen, optionally substituted C_{1-8} alkyl, or C_{1-8} alkoxy;

m is 0 or an integer having a value of 1 or 2;

R_3 is $S(O)_2R_7$;

R_4 is hydrogen or $S(O)_2R_7$;

10 R_5 is hydrogen, halogen, CF_3 , CH_3 , $(CH_2)_tC(O)_2R_9$, or $(CH_2)_tOH$;

t is 0 or an integer having a value of 1 or 2;

R_6 is hydrogen or halogen;

R_7 is optionally substituted aryl, optionally substituted aryl- C_{1-2} alkyl, or an optionally substituted C_{1-8} alkyl;

15 R_8 is hydrogen or C_{1-4} alkyl;

R_9 is hydrogen or C_{1-4} alkyl;

or a pharmaceutically acceptable salt thereof.

R_1 is suitably $(CH_2)_nOH$ or $(CH_2)_nCO_2R_8$. Preferably R_1 is

$(CH_2)_nCO_2R_8$ and n is preferably 0. R_8 is preferably hydrogen or methyl, more

20 preferably hydrogen, or a pharmaceutically acceptable salt thereof.

Suitably, R_2 is independently a substituent on the benzene ring from 1 to 2

times, and such substituent is selected from hydrogen, halogen, an optionally substituted C_{1-8} alkyl, or C_{1-8} alkoxy group. Suitably when R_2 is halogen it is a

chlorine, bromine, fluorine or iodine. When R_2 is an optionally substituted C_{1-8}

25 alkyl, the alkyl is substituted one to three times with halogen, such as fluorine,

preferably a trifluoromethyl group. The optionally substituted C_{1-8} alkyl moiety if

preferably a branched C_5 chain, such as 1,1-dimethyl propyl moiety or a C_8

branched chain such as 1,1,3,3-tetramethyl butyl moiety.

Suitably, R_3 is $S(O)_2R_7$; and R_7 is an optionally substituted aryl, an

30 optionally substituted aryl- C_{1-2} alkyl, or an optionally substituted C_{1-8} alkyl group.

Preferably when R_7 is an aryl moiety it is phenyl or naphthyl, preferably phenyl;

when R7 is an aryl alkyl moiety it is preferably benzyl. Suitably the aryl, aryl alkyl or alkyl moieties are substituted independently, one to three times, by halogen, trifluoromethyl, aryloxy, methoxy, CH₂OH, methyl, or C(O)₂H. Preferably, the substituents are halogen, or trifluoromethyl. The substituent halogen groups are preferably Cl, Br and fluorine. Preferably the substituents are in the 3,5- position or the 4-position of the aryl ring. More preferably the aryl substituents are 3,5-bis-trifluoromethyl, 4-trifluoromethyl, 4-bromo, 4-chloro, or 4-fluoro.

When R7 is an optionally substituted alkyl moiety it is preferably a methyl or a C₈ unbranched chain. The methyl moiety, if substituted, is preferably substituted by one or more fluorines, such as in a trifluoromethyl group.

R4 is suitably hydrogen or S(O)₂R7. Preferably R4 is hydrogen. When R4 is S(O)₂R7 the R7 group is preferably the same R7 moiety as in the R3 group forming a bis structure.

Suitably R5 is hydrogen, halogen, CF₃, CH₃, CH₂C(O)₂R9, or CH₂OH, wherein t is 1. Preferably when R5 is CH₂C(O)₂R9, R9 is a C₁₋₄ alkyl, preferably t-butyl. Preferred R5 groups are hydrogen, CF₃, or halogen. More preferably R5 is hydrogen or CF₃.

Suitably R6 is hydrogen or halogen; preferably hydrogen. If R6 is halogen it is preferably fluorine or chlorine.

Additional compounds for use herein as PLA₂ inhibitors are found in U.S. Patent 5,470,882, Dixon et al., granted November 28, 1995; WO95/33712, Dixon et al., published December 14, 1995; U.S. Patent 5,545,669, Adams et al., granted August 13, 1996; WO95/33461, Adams et al., published December 14, 1995; WO95/33462, Adams et al., published December 14, 1995; U.S. Patent 5,447,957, Adams et al., granted September 5, 1995; WO95/33460, Adams et al., published December 14, 1995; WO95/33458, Adams et al., published December 14, 1995; WO95/33713, Adams et al., published December 14, 1995; WO95/33715, Eggleston et al., published December 14, 1995; U.S. Patent 5,496,855, Adams et al., granted March 5, 1996; WO96/22770, Adams et al., published August 1, 1996.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of formula (I) may also be formed with a pharmaceutically acceptable

cation, for instance, if substituent R₁ comprises a carboxy group. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

- 5 • "halo" - all halogens, that is chloro, fluoro, bromo and iodo;
- "C₁₋₈ alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 8 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like;
- 10 • "aryl" - phenyl and naphthyl;
- "aryl alkyl" - is used herein to mean a phenyl and naphthyl connected to a C₁₋₄ alkyl as defined above unless otherwise indicated;

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

Specifically exemplified compounds of Formula (I) for use herein are:

- 2-[2-[3,5-bis(trifluoromethyl)phenylsulfonamido]-4-trifluoromethylphenoxy]benzoic acid;
- 2-[2-(4-Bromophenylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;
- 20 2-[2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]phenoxy]benzoic acid;
- 2-[2-(2-Naphthylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;
- 2-[2-(2-Naphthylsulfonamido)phenoxy]benzoic acid;
- 2-[2-[3,5-Bis(trifluoromethyl)phenyl]sulfonamido-4-trifluoromethylphenoxy]-5-(1,1-dimethylpropyl)benzoic acid;
- 25 2-[2-(Octylsulfonamido)phenoxy]benzoic acid; (also referred to as
- 2-[2-[(Octylsulfonyl)amino]phenoxy]benzoic acid);
- 2-[2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]-4-methylphenoxy]benzoic acid;
- 2-[2-[(Methylsulfonyl)amino]-4-(trifluoromethyl)phenoxy]benzoic acid;
- 2-[2-[(Octylsulfonyl)amino]-4-(trifluoromethyl)phenoxy]benzoic acid;
- 30 2-[2-[3,5-bis(trifluoromethyl)phenyl-N-methylsulfonamido]-4-trifluoromethylphenoxy]benzoic acid;
- 2-[2-(Phenylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;
- 2-[2-(4-Chlorophenylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;
- 2-[2-(1-Naphthylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;
- 35 2-[2-(Phenylmethylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;
- 2-[2-(4-Trifluoromethylphenylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;

- 2-[2-[3,5-bis(Trifluoromethyl)phenylsulfonamido]-4-trifluoromethylphenoxy]phenylacetic acid;
 2-[2-(4-Fluorophenylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;
 2-[2-(4-Methoxyphenylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;
 5 2-[2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]-4-(trifluoromethyl)-phenoxy]-4-methoxybenzoic acid;
 2-[2-[N,N-Bis[3,5-bis(trifluoromethyl)phenylsulfonyl]amino]-4-(trifluoromethyl)phenoxy]-4-methoxybenzoic acid;
 2-[2-[N,N-Bis-[3,5-bis(trifluoromethyl)phenylsulfonyl]amino]-4-(trifluoromethyl)phenoxy]benzoic acid;
 10 2-[2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]-4-bromophenoxy]benzoic acid;
 2-[2-[[[3,5-Bis(trifluoromethyl)phenyl]sulfonyl]amino]-4-bromo-phenoxy]benzoic acid;
 15 2-[2-(4-Hydroxymethylsulfonamido)-4-trifluoromethylphenoxy]benzoic acid;
 6-[2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]-4-trifluoromethylphenoxy]-2-methoxybenzoic acid;
 2-[2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]-4-trifluoromethylthiophenoxy]benzoic acid;
 20 2-[2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]-4,5-dichloro-phenoxy]benzoic acid;
 2-[2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]-4-trifluoromethylphenoxy]benzyl alcohol;
 2-[2-(4-Chlorophenylsulfonamido)-4,5-dichlorophenoxy]benzoic acid;
 25 2-[2-(4-Bromophenylsulfonamido)-4-(carboxymethyl)phenoxy]benzoic acid;
 2-[2-(4-Bromophenylsulfonamido)-4-(hydroxyethyl)phenoxy]benzoic acid;
 Methyl 2-[2-(4-Bromophenylsulfonamido)-4-(carboxymethyl)-phenoxy]benzoate;
 2-[2-(4-Bromophenylsulfonamido)-4-(tert-butoxycarbonylmethyl)-phenoxy]benzoic acid;
 30 2-[2-[(Trifluoromethylsulfonyl)amino]-4-(trifluoromethyl)phenoxy]benzoic acid;
 2-[trans-2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]cyclohexyloxy]benzyl alcohol; and
 2-[trans-2-[3,5-Bis(trifluoromethyl)phenylsulfonamido]cyclohexyloxy]benzoic acid.

In order to use a compound of formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention,

therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of formula (I), pharmaceutically acceptable salts thereof and
5 pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of formula (I) may be administered in conventional dosage forms prepared by combining a compound of formula (I) with standard pharmaceutical carriers according to conventional
10 procedures. Such pharmaceutically acceptable carriers or diluents and methods of making are well known to those of skill in the art, and reference can be found in such texts as Remington's Pharmaceutical Sciences, 18th Ed., Alfonso R. Genarao, Ed., 1990, Mack Publishing Co. and the Handbook of Pharmaceutical Excipients, APhA Publications, 1986.

The compounds of formula (I) may also be administered in conventional dosages in combination with known second therapeutically active compounds, such as steroids or NSAID's for instance. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the
20 pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl
30 mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When
35 a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft

gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100 °C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compounds of the invention will normally be administered to a subject in a daily dosage regimen. For an adult patient this may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered from 1 to 4 times per day.

The choice of form for administration, as well as effective dosages, will vary depending, inter alia, on the condition being treated. The choice of mode of administration and dosage is within the skill of the art.

Chronic diseases which have an inappropriate angiogenic component are various ocular neovascularizations, such as diabetic retinopathy and macular degeneration.

Other chronic diseases which have an excessive or increased proliferation of vasculature are tumor growth and metastasis, atherosclerosis, and certain arthritic conditions. Therefore cytokine inhibitors will be of utility in the blocking of the angiogenic component of these disease states.

The term "excessive or increased proliferation of vasculature inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by hemangiomas and ocular diseases.

The term "inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by vesicle proliferation with accompanying tissue proliferation, such as occurs in cancer, metastasis, arthritis and atherosclerosis.

Described below a model of inflammatory angiogenesis is used to show that PLA_2 inhibition will stop the tissue destruction of excessive or inappropriate proliferation of blood vessels. Based on these observations, a PLA_2 inhibitor, 2-[2-[3,5-bis(Trifluoromethyl)-phenylsulfonamido]-4-trifluoromethylphenoxy]benzoic acid, Compound I, was tested for its ability to inhibit angiogenesis in an *in vivo* animal model of inflammatory angiogenesis.

The murine airpouch granuloma model of chronic inflammation (Kimura et al., 1985, J. Pharmacobio-Dyn., 8:393-400; Colville-Nash et al., 1995, J. Pharm. and Exp. Ther., 274:1463-1472) whose disclosure is incorporated herein by reference in its entirety, is characterized by inflammatory cell influx, fibrous tissue proliferation and intense angiogenesis. It is representative of inflammatory angiogenesis and demonstrates that the angiogenic component can be pharmacologically modulated independently of granuloma growth and size. In addition, angiogenesis can be accurately quantitated by a vascular casting method.

The effect of the compound on vascular density (and dry weight) was measured for 6 days after induction of the granuloma. This time point has been determined to be at or near the peak of angiogenesis. Compound I demonstrated a significant decrease in the vascular index with a maximum reduction of 36% at 30mg/kg, bid, i.p. As a positive control medroxyprogesterone, an angiostatic steroid (Gross et al., 1981, Proc. Natl. Acad. Sci. USA, 78:1176-1180) - whose disclosure is hereby incorporated by reference in its entirety, was utilized. This control demonstrated a maximum reduction of 50% in this model. Neither Compound I nor medroxyprogesterone had an effect on granuloma size as measured by dry weight.

Angiogenesis in the granuloma was microscopically evaluated. The vasculature of day 6 granulomas from both untreated and compound I treated mice was examined. The profound angiogenesis in the granuloma is demonstrated by the extensive vascular network in the control tissue. There was a striking reduction in the vasculature of the treated tissue. In fact, there was almost no fine capillaries visible, only a few larger vessels.

Prostanoids and leukotrienes are the downstream products of the arachidonic acid released by PLA₂. The levels of these lipid mediators in the granuloma were measured to determine if there modulation by compound I correlated with angiogenesis. Prostaglandin D₂ (PGD₂) and leukotriene B₄ (LTB₄) levels were measured by ELISA using homogenates of day 6 granuloma tissue. LTB₄ was measured at 3404 pg/ml in vehicle treated animals and 2042 pg/ml in compound I treated animals. Thus compound I reduced LTB₄ levels by 40 %. In contrast, PGD₂ levels were not affected by compound I, 378 pg/ml PGD₂ in vehicle treated animals and 403 pg/ml PGD₂ in compound I treated animals. These results are consistent with specific inhibition of 14 kD PLA₂ by compound I in vivo, because 14 kD PLA₂ releases arachidonic acid for leukotriene synthesis, while arachidonic acid used for prostaglandin synthesis is released by 85 kD PLA₂.

Methods:

Murine air pouch granuloma model:

Day -1, mice are anesthetized using Aerrane (isoflurane) gas (5%), after which 3mls of air is injected into the dorsal subcutaneous tissue using a 27g needle. Mice are allowed to recover.

Day 0, mice are again anesthetized using Aerrane, once anesthetized 0.5ml of Freund's complete adjuvant with 0.1% v/v croton oil is injected into the air pouch formed on Day -1. The animals also begin their dosing regime (number of days dependent upon study) with the animals typically receiving compound in 0.2ml N,N, Dimethyl Acetoacetamide(DMA)(Sigma, St. Louis, Mo.)/Cremephor El (Sigma, St. Louis, Mo.)/ saline (10/10/80) or other appropriate vehicle. The animals are allowed to recover and all subsequent dosing is performed on the animals in the absence of anesthetics.

Days 1-5, animals are dosed according to schedule.

On Day 6 the animals are again anesthetized using Aerrane after which a vascular cast is made (Kimura et al., 1986, J.Pharmacobio-Dyn., 9:442-446), this involves a 1ml tail vein i.v. injection of a Carmine Red(10%)(Sigma, St. Louis, Mo.)/ gelatin (5%)(Sigma, St. Louis, Mo.) solution. The animals are then sacrificed by lethal dose of anesthesia and chilled at 4 C for 2 hours prior to the removal of the granuloma tissue.

When the granuloma is removed it is weighed and then dried for 3 days at 45 C and reweighed. The dried tissue is then digested in 0.9ml of a 0.05M phosphate

buffer pH 7.0 containing 12 U /ml⁻¹ papain (Sigma, St. Louis, Mo.) and 0.33g / L⁻¹ N-acetyl-L-Cysteine (Sigma, St. Louis, Mo.) at 57 C for 3 days. After 3 days digestion the carmine red is solubilized by the addition of 0.1ml 5mM NaOH. Samples are centrifuged and then filtered using 0.2um acrodiscs. The carmine content is then determined against a carmine red standard curve (0.5 to 2 mg/ml) generated in extracted tissue from non carmine treated animals and read at 490nm. Sample and standard values are determined using DeltaSoft Elisa analysis software (Biometallics Inc., Princeton, NJ). The carmine content is then used to determine the vascular indexes for the various treatments, vascular index being the mg carmine dye/gm dry tissue.

Tissue extracts were made by homogenizing granulomas in 0.5ml 5mM KH₂PO₄ / 0.1gm wet tissue. PGD₂ and LTB₄ were measured using ELISA kits from Cayman Chemical Company. Sample values for both ELISAs are calculated using DeltaSoft ELISA analysis software (Biometallics Inc., Princeton, NJ).

Figure 1 shows the tissue dry weight and vascular index (VI, mg carmine dye/ gm dry tissue) of Day 6 granulomas following treatment with compound I or medroxyprogesterone. Dosing began at the time granulomas were induced. VI data is expressed as a percent of vehicle treated control animals +/- S.D. Control VI=4.6. control dry weight=0.25 gms. n=5. * significant from control at p<0.05, calculated by Duncan's multiple range test.

To determine PLA₂ activity of the compounds for use herein various cellular assays can be used. Additionally, various classical in vivo acute inflammatory models which have some aspect of their etiology to elevated eicosanoid levels can be employed, such as the paw edema model, mouse zymosan peritonitis, reverse Arthus pleurisy or various skin inflammation assays which are described in Lewis et al., Experimental Models of Inflammation, in the Handbook of Inflammation, Vol. 5, Bonta Ed., Elsevier Science Publishers, NY (1985) whose disclosure is herein incorporated by reference. The TPA induced ear edema model (mouse) as well as the carrageenan paw edema model in the rat are described herein as well. These classical models of inflammation will reflect the drug's ability to alter an inflammatory response but cannot address the specificity of drug action. These models have been traditionally designed as non steroid antiinflammatory drug sensitive pharmacological screens and it is important to utilize models which can differentiate PLA₂ from NSAIDS, such as described below.

Phospholipase A₂ assay:

Phospholipase A₂ activity of rh Type II- 14 kDa PLA₂ or PLA₂ semi-purified from human synovial joint fluid was measured by the acylhydrolysis of high specific activity (NEN)[³H]-AA-*E. coli* (0.5 mCi/5nmol PL Pi) as previously described in Marshall et al., J. Rheumatology, 18:1, pp59-65 (1991). High specific activity [³H]AA-*E. coli* had up to 95% of the label incorporated into phospholipid which was localized almost exclusively in the sn-2 position, as demonstrated by purified 14kDa PLA₂ or low molecular weight PLA₂ acylhydrolysis and separation of products by thin layer chromatography (TLC) (data not shown). [Predominately used herein was rh Type II 14 kDa PLA₂, or alternatively bovine pancreatic PLA₂ was also be used]. The reaction mixture (50 or 100 ml total volume) contained 25 mM HEPES, pH 7.4, 150 mM NaCl, 5 mM CaCl₂ and [³H]-AA-*E. coli* (low specific activity; 5-8 nmol PL Pi per assay). Assays were incubated for a time predetermined to be on the linear portion of a time versus hydrolysis plot. Experiments were conducted with final % hydrolysis values ranging from 2% (400-1000 dpm) to 10% (2000-5000 dpm) acylhydrolysis after blank correction. Reactions were terminated by the addition of 1.0 mL tetrahydrofuran (THF). The whole sample was placed over aminopropyl solid phase silica columns and eluted with THF:acetic acid (49:1) exclusively separating free fatty acids with greater than 95% recovery. Radiolabel in this eluate was quantitated by liquid scintillation counting. Results were expressed as % of fatty acid hydrolyzed ([sample dpms - non-specific (blank) dpms/total dpms] x 100) or specific activity which was calculated from hydrolysis values found in the linear portion of time versus % hydrolysis plots (pmol free fatty acid hydrolyzed/mg/min). Non-specific activity was always less than 1% of the total counts added.

Protein Determination

All protein concentrations were determined by Bradford protein analysis kits (Biorad, Richmond, CA). All of the exemplified compounds of Formula (I) described herein demonstrated positive PLA₂ inhibition in the method noted above. While these compounds generally tested positive at 50 µm levels, several were also tested for positive inhibitory activity at up to 500 µm levels.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

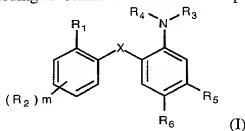
The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples

5 herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

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What is Claimed is:

1. A method of treating a chronic disease in a mammal in need thereof, which disease is characterized by excessive, undesired or inappropriate angiogenesis, with an effective amount of a compound which inhibits the production, transcription, translation, or activity of 14 kDa PLA₂.
2. The method according to Claim 1 wherein the disease is diabetic retinopathy and other ocular neovascularizations.
3. The method according to Claim 1 wherein the disease is tumor growth and metastasis.
4. The method according to Claim 1 wherein the disease is atherosclerosis.
5. The method according to Claim 1 wherein the compound is of the formula:



wherein

R₁ is (CH₂)_nOH or (CH₂)_nCO₂R₈;

n is 0 or an integer a value of 1;

X is oxygen or sulfur;

R₂ is hydrogen, halogen, optionally substituted C₁₋₈ alkyl, or C₁₋₈ alkoxy;

m is 0 or an integer having a value of 1 or 2;

R₃ is S(O)₂R₇;

R₄ is hydrogen or S(O)₂R₇;

R₅ is hydrogen, halogen, CF₃, CH₃, (CH₂)_tC(O)₂R₉, or (CH₂)_tOH;

t is 0 or an integer having a value of 1 or 2;

R₆ is hydrogen or halogen;

R₇ is optionally substituted aryl, optionally substituted arylC₁₋₂ alkyl, or an

optionally substituted C₁₋₈ alkyl;

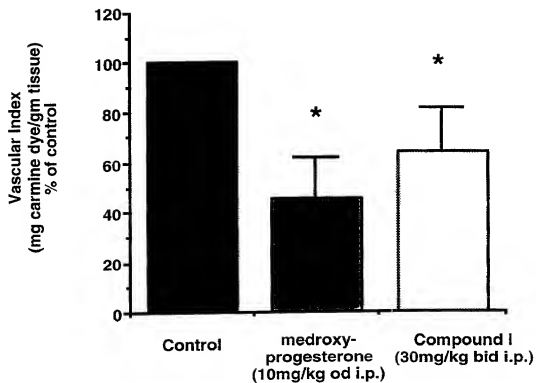
R₈ is hydrogen or C₁₋₄ alkyl;

R₉ is hydrogen or C₁₋₄ alkyl;
or a pharmaceutically acceptable salt thereof.

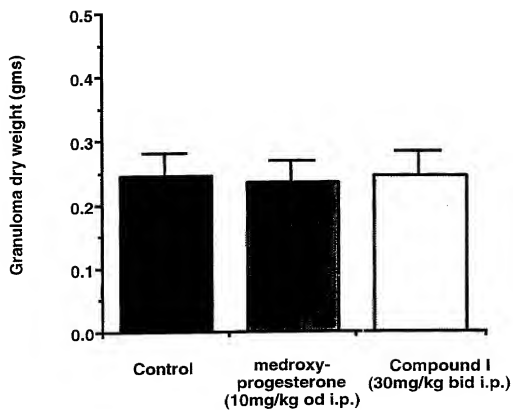
6. The method according to Claim 5 wherein the compound is 2-[2-[3,5-
5 bis(trifluoromethyl)phenylsulfonamido]-4-trifluoromethylphenoxy]benzoic acid, or
a pharmaceutically acceptable salt thereof.

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1A



1B



DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"PLA2 Inhibitors of Angiogenesis"

the specification of which (check one)

☐ is attached hereto.

☒ was filed on **26 March 1997** as Serial No. **PCT/US97/04876**
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
60/014,244	26 March 1997

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

09142033.091005

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

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Address all correspondence and telephone calls to Dara L. Dinner, SmithKline Beecham Corporation, Corporate Intellectual Property-U.S., UW2220, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939, whose telephone number is 610-270-5017.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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